

RETICULOENDOTHELIAL SYSTEM AND FUNCTIONS OF THE SPLEEN

Nonspecific Host Defenses

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OBJECTIVES

At the end of this lecture you should be able to:

- ▶ **Describe Monocyte macrophage system (RES)**
- ▶ **Functions of monocytes/macrophages in different tissues**
- ▶ **Mechanism of chemotaxis, phagocytosis and microbial killing**
- ▶ **Explain functions of spleen**
- ▶ **Understand the basic concept of the indications and risks of splenectomy.**

IMMUNITY

```
graph TD; A[IMMUNITY] --> B["Innate immunity  
(non specific)"]; A --> C["Acquired immunity  
(specific, adaptive)"]; B --> D["Phagocytes  
(Neut, Mono, NK)"]; B --> E["Complement"]; B --> F["Barriers"]; C --> G["Cell mediated  
T lymphocytes"]; C --> H["Humoral  
Antibody  
mediated  
B lymphocytes"];
```

Innate immunity

(non specific)

Examples:

- Phagocytes
(Neut, Mono, NK)
- Complement
- Barriers

Acquired immunity

(specific, adaptive)

Cell mediated
T lymphocytes

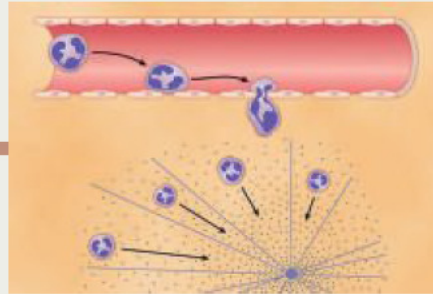
Humoral
Antibody
mediated
B lymphocytes

Note: Macrophages are key components of the innate immunity and activate adaptive immunity by transforming into Antigen Presenting Cells

Innate immunity
(non specific)

Examples:

- Phagocytes
- Complement
- Barriers



CHAPTER 34

Resistance of the Body to Infection: I. Leukocytes, Granulocytes, the Monocyte-Macrophage System, and Inflammation

UNIT VI

Acquired immunity
(specific, adaptive)



CHAPTER 35

Resistance of the Body to Infection: II. Immunity and Allergy

UNIT VI

RETICULOENDOTHELIAL SYSTEM

It is a network of connective tissue fibers inhabited by phagocytic cells such as macrophages ready to attack and ingest microbes.

- ❑ Monocytes transform themselves into macrophages in tissue & this system of phagocytes is called as **Monocyte-Macrophage Cell System**
- ❑ RES term is old although they are neither reticular in appearance nor they have endothelial origin just these phagocytic cells are located in reticular connective tissue
- ❑ Therefore, the term reticuloendothelial system is not used nowadays.

Reticuloendothelial System Monocyte/Macrophage System

TISSUE MACROPHAGE SYSTEM COMPONENTS

3

- Monocytes in **Blood**
- Mobile & Fixed Macrophages in **Tissue**
- **Specialized endothelial cells** in bone marrow, spleen and lymph nodes

German pathologist Karl Albert Ludwig Aschoff introduced the term reticuloendothelial system in 1924,

General Functions of RES

1. **Phagocytosis**: Bacterial, dead cells, foreign particles (**direct**).
2. **Immune function**: processing antigen and antibodies production (**indirect**).
3. **Breakdown** of aging RBC.
4. **Storage** of RBC and and recycling **iron**.

WBCs Concentration (Normal Counts)

Cells	Approximate Normal range (/μL)	Percentage of Total WBC	Life Span
Total WBC	4000-11000	- - -	
Granulocytes • Neutrophils • Eosinophils • Basophils	3000-6000 150-300 0-100	50-70% 1-4% 0.4	4-8 hours in blood and 4-5 days in tissues
Lymphocytes	1500-4000	20-40%	Weeks-months
Monocytes (macrophages)	300-600	2-8%	10-20 hours (months)

Polymorphonuclear neutrophils	62.0%
Polymorphonuclear eosinophils	2.3%
Polymorphonuclear basophils	0.4%
Monocytes	5.3%
Lymphocytes	30.0%

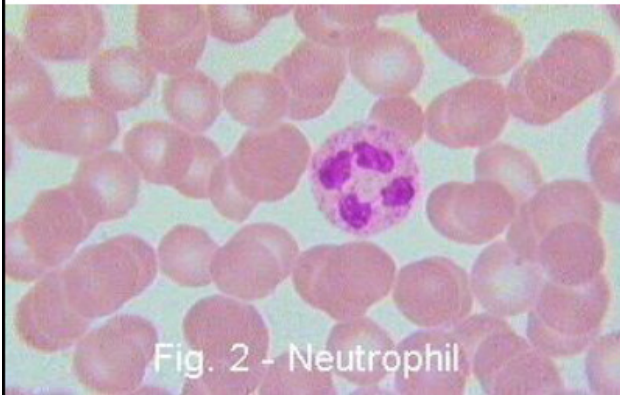


Fig. 2 - Neutrophil

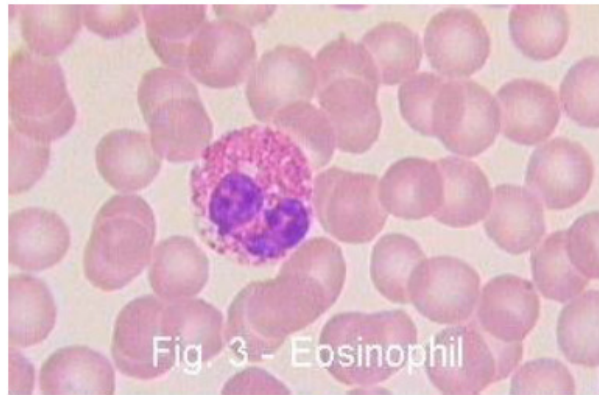


Fig. 3 - Eosinophil

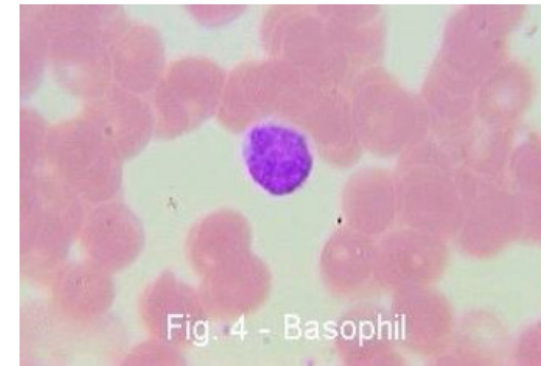


Fig. 4 - Basophil

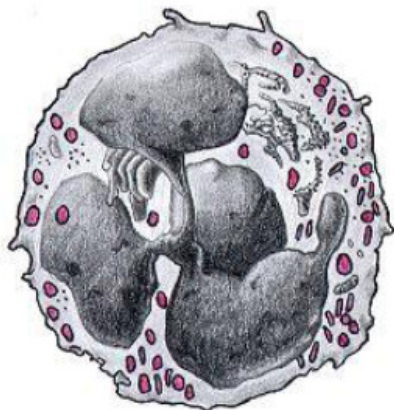


Fig. 8 - Neutrophil

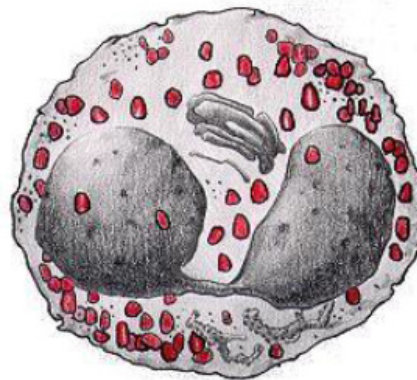


Fig. 9 - Eosinophil

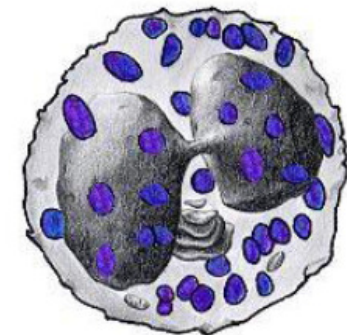


fig. 10 - Basophil

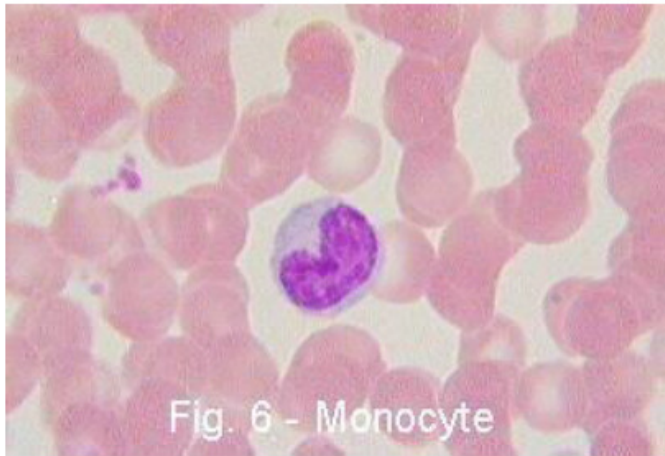


Fig. 6 - Monocyte

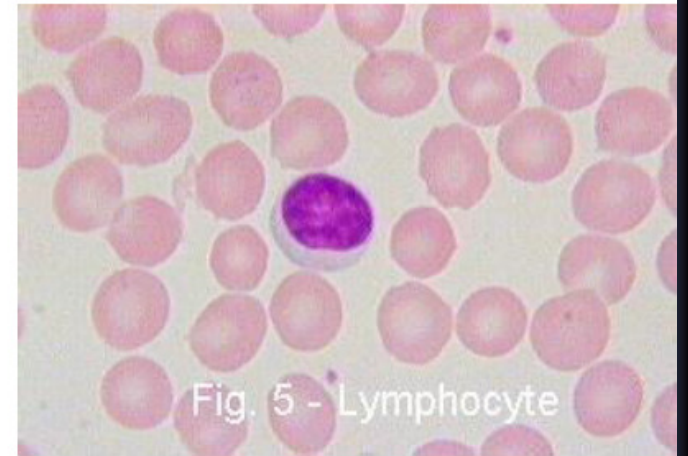


Fig. 5 - Lymphocyte

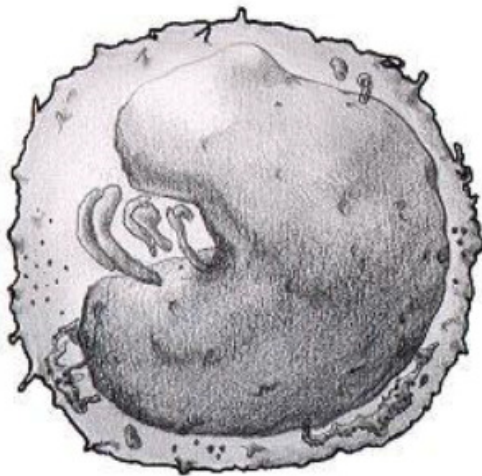


Fig. 12 - Monocyte



Fig. 11 - Lymphocyte

Responses During Inflammation

Macrophage and Neutrophil

- ❑ **1st** line of defense – **Tissue macrophages & Physical Barriers**
- ❑ **2nd** line of defense – Neutrophil Invasion of the inflamed area
- ❑ **3rd** line of defense – **Monocytes –macrophage invasion of inflamed area**
- ❑ **4th** line of defense – Increased production of granulocytes and Monocytes by Bone marrow

DEFENSIVE PROPERTIES OF MACROPHAGES & NEUTROPHILS

- **Margination:** WBC Roll, Bind and then stick along the walls of blood capillaries
- **Diapedesis:** WBC squeezes itself through endothelial holes leaving blood capillaries
- **Chemotaxis:** WBC move by amoeboid motion towards inflammation area following chemotactic substances (Bacterial toxins, Complement [C5a], LKB4) are released from site of infection
- **Phagocytosis:** Upon reaching the site of infection neutrophils start to engulf infecting organism

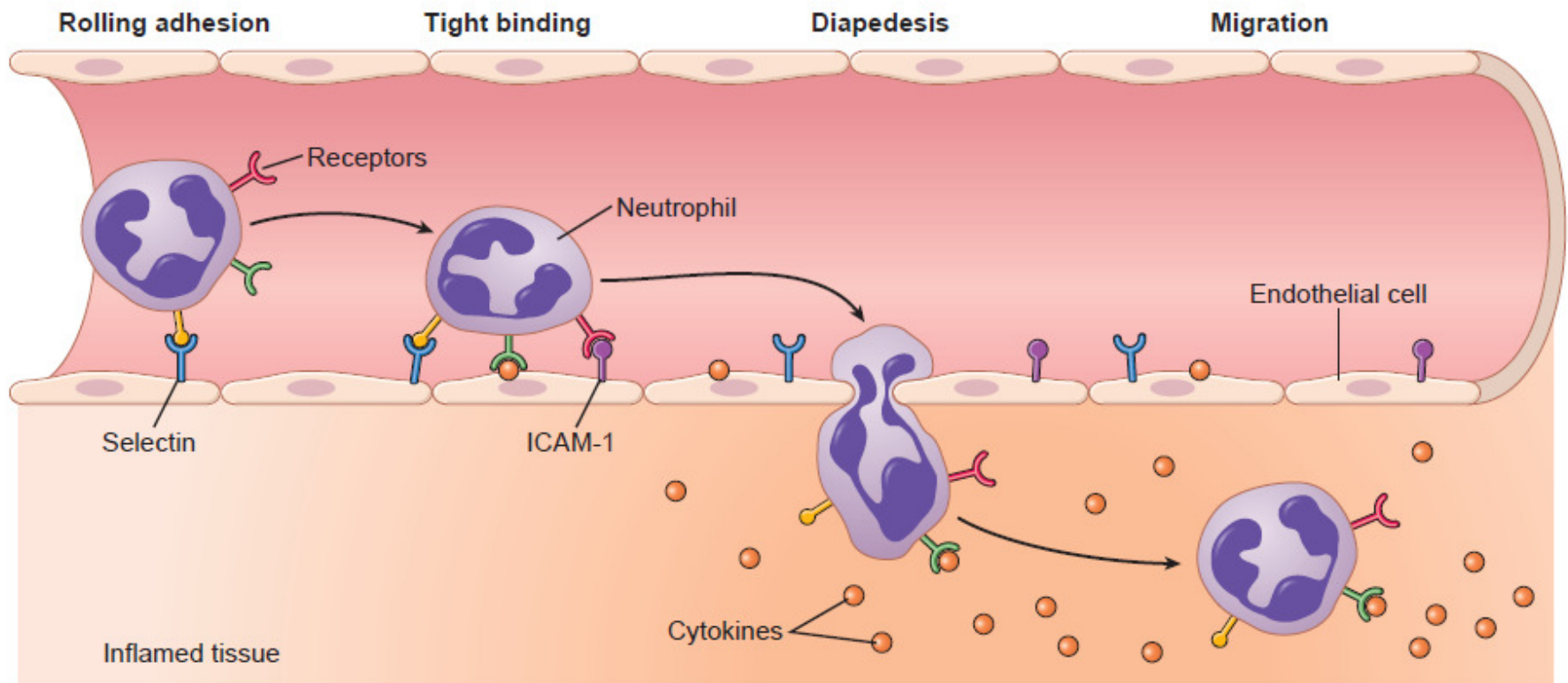
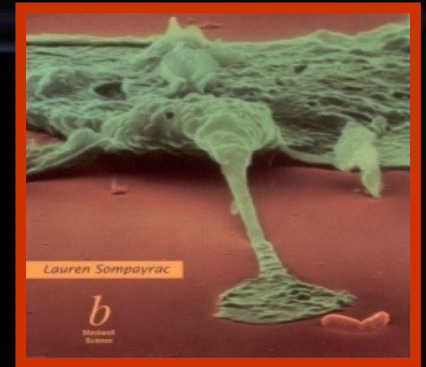


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 (*ICAM-1*) in the surface of endothelial cells. These adhesion molecules bind to complementary molecules/receptors on the neutrophil, causing it to adhere to the wall of the capillary or venule. The neutrophil then migrates through the vessel wall by diapedesis toward the site of tissue injury.

MONOCYTES



- **Size:** 15-20 μm (active cells 60-80 μm)
- **Small Granules (Prim) & Vacoules**
- **More Efficient Phagocytosis** than Neutrophils (100 bacteria vs 3-20 by Neutr, larger particles like RBCs & malarial parasites)
- **Life span:** 10-20 hours in blood...& in tissues?
- **Two types:** Mobile & Fixed
- Lysosomes contain **lipases** unlike Neutrophils.
- Acts as **Antigen Presenting Cells**

QUICK REVIEW:

CELLS OF THE RES OR TISSUE MACROPHAGE SYSTEM

Descriptions	Locations
Fixed macrophages: (reticulum cells) large cells, small nucleus	Spleen, lymph nodes, bone marrow, liver, skin (histiocytes), lungs (macrophages), etc.
Free macrophages: large wandering cells	Spleen, lymph nodes, lungs, many other tissues
Circulating monocytes: large, motile cells with indented nuclei	Blood

NEUTROPHILS

- Most Abundant WBCs 60-70 %
- Size: 15-20 μm
- Nucleus: Multilobed 2-5 lobes
- Life span: 6-8 hours

NEUTROPHIL GRANULES

- Primary Granules (Non Specific, Azurophilic, lysosomes) [33%]:

Acid hydrolases, MPO, HOCl, Defensins

- Secondary Granules (Specific) [67%]:

Lysozyme, Lactoferrin, Alkaline Phosphatase, Gelatinase, Bacteriostatic & Bactericidal products.

- Tertiary Granules : (help to digest tissues)
Collagenase, Hyaluronidase and Gelatinase.

POOLS:

Bone Marrow, Circulating and Marginated Pool

PolyMorphoNuclear leucocytes

MONOCYTES
CONTAIN
PRIMARY
GRANULES AND
VACUOLES

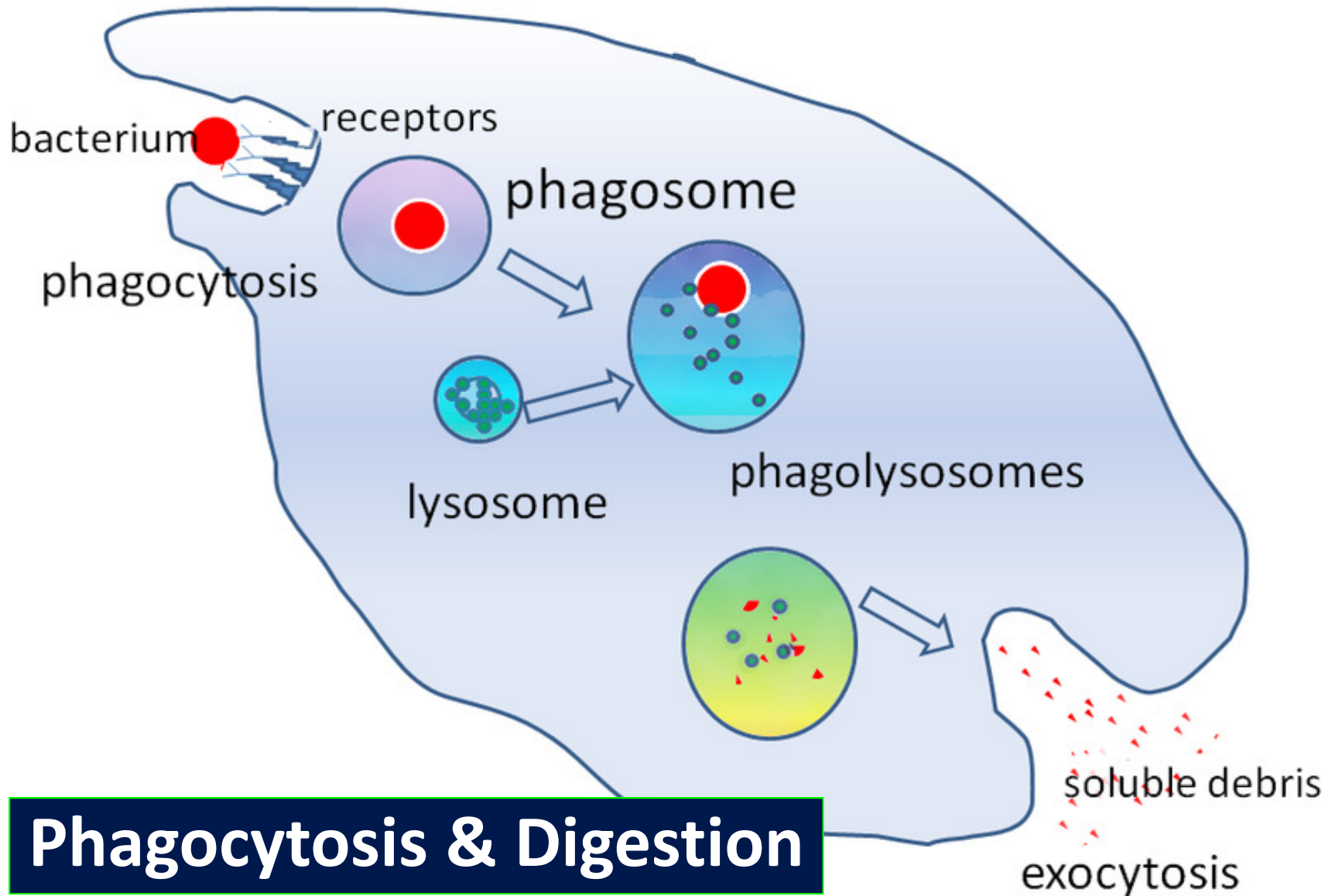
prim
(azurophilic)

(specific)

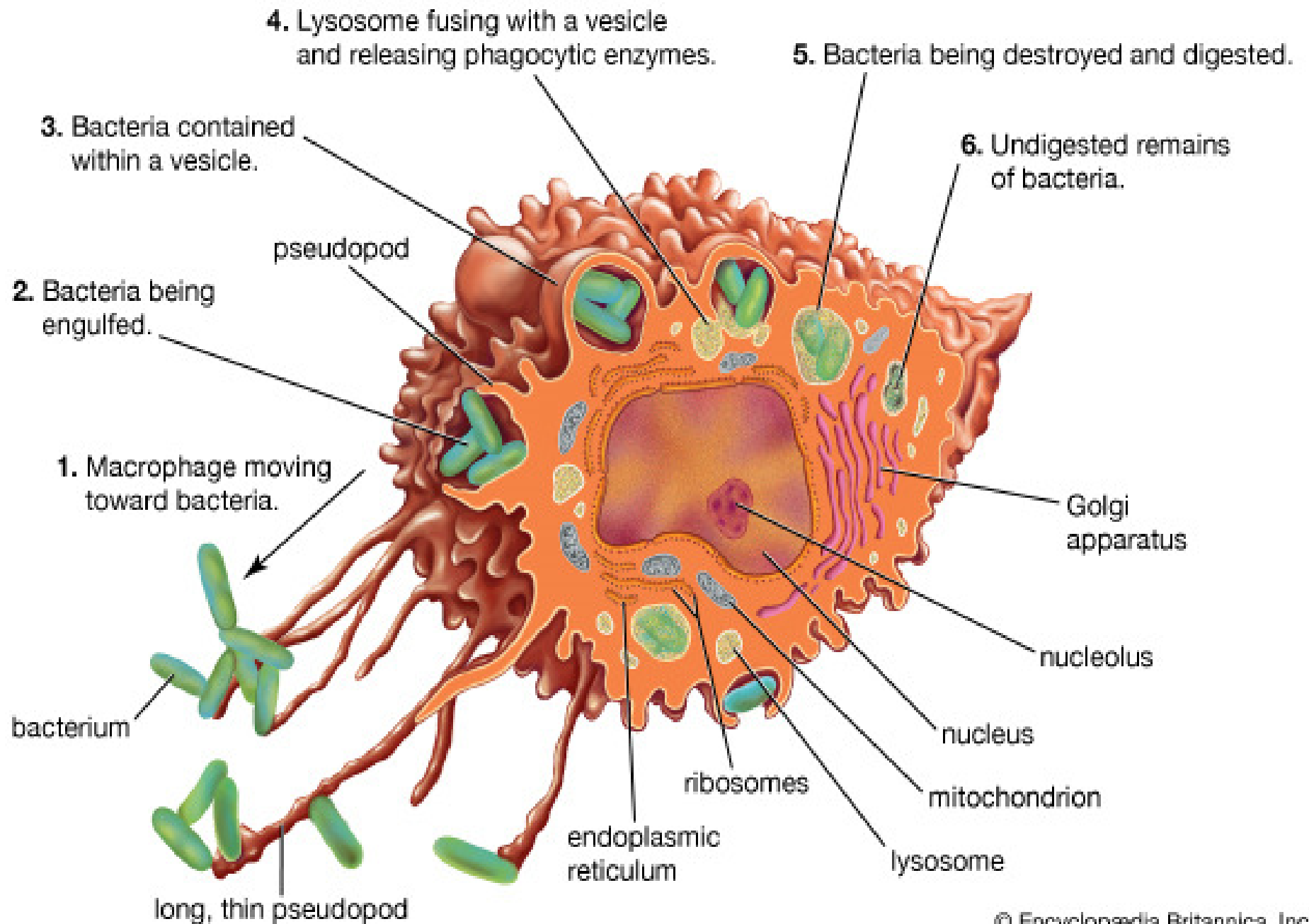
tertiary granules

Glycogen granules: for anaerobic glycolysis.

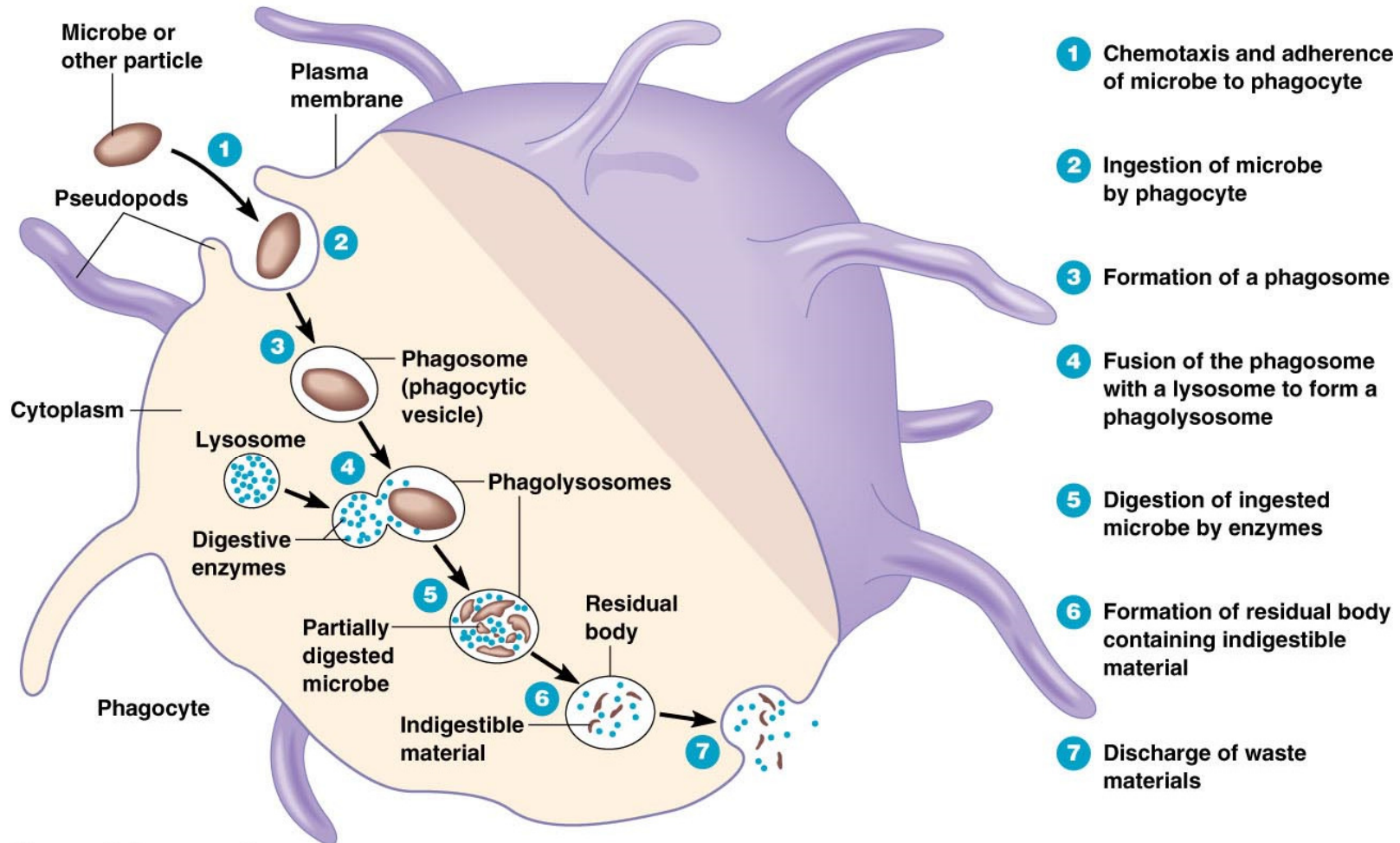
Direct function of RES



Phagocytosis & Digestion



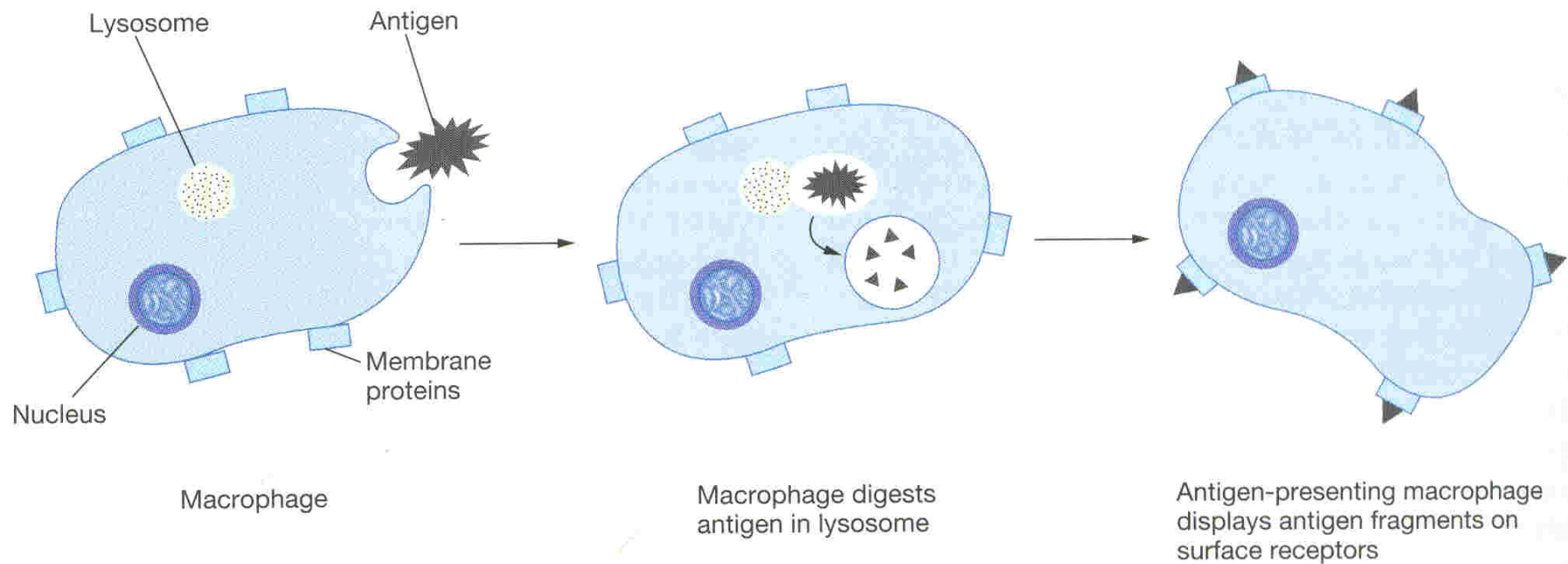
Macrophage: a wandering, walking cell. “Big eater” capable of phagocytosis. Is a modified monocyte in tissues



Phases of phagocytosis

Indirect Immune function Of RES

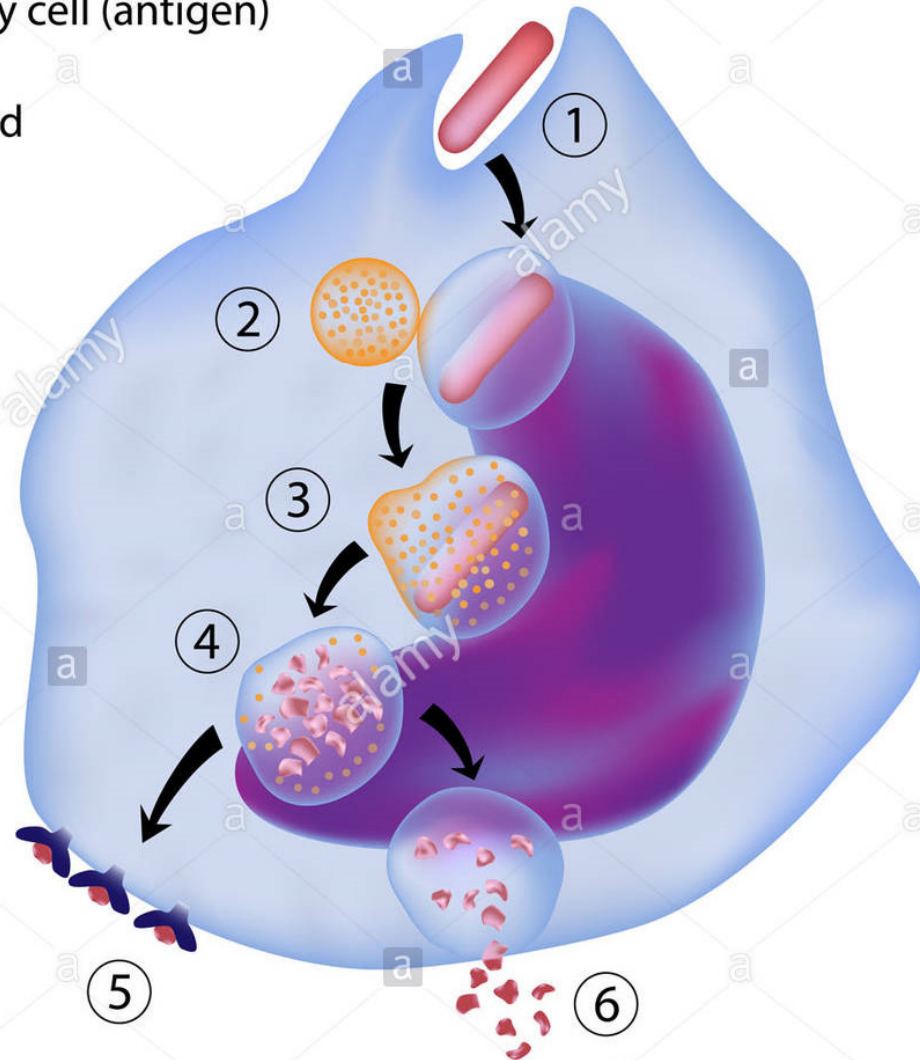
Antigen Presenting Cells



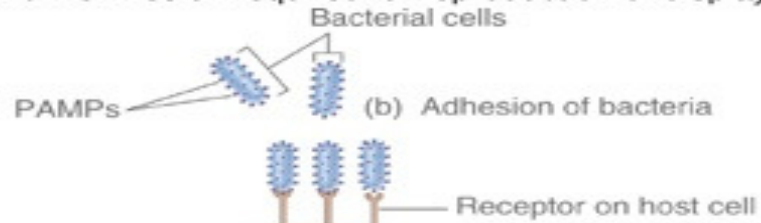
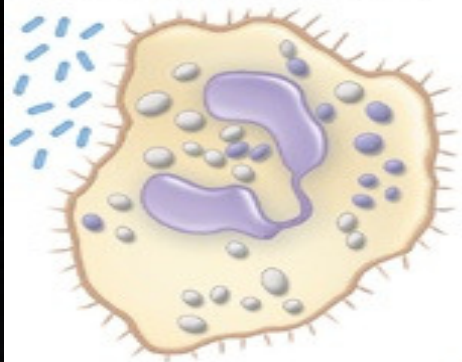
Displaying it attached to an MHC class II molecule

Role of an Antigen-Presenting Cell

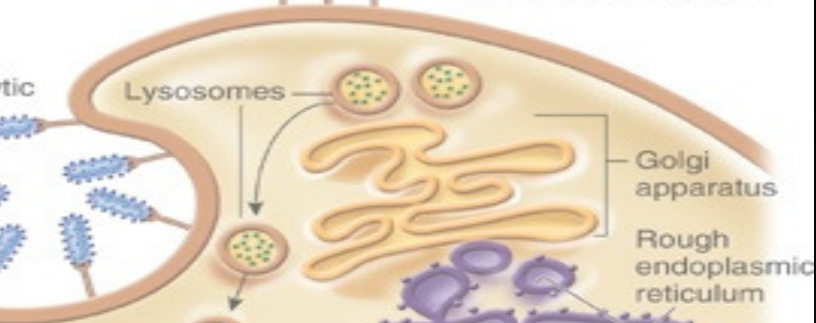
- ① Phagocytosis of enemy cell (antigen)
- ② Fusion of lysosome and phagosome
- ③ Enzymes start to degrade enemy cell
- ④ Enemy cell broken into small fragments
- ⑤ Fragments of antigen presented on APC surface
- ⑥ Leftover fragments released by exocytosis



(a) Chemotaxis by phagocyte



(c) Engulfment into phagocytic vacuole



(d) Phagosome



(e) Phagolysosome formation



(f) Killing and destruction of bacterial cells



(g) Release of residual debris

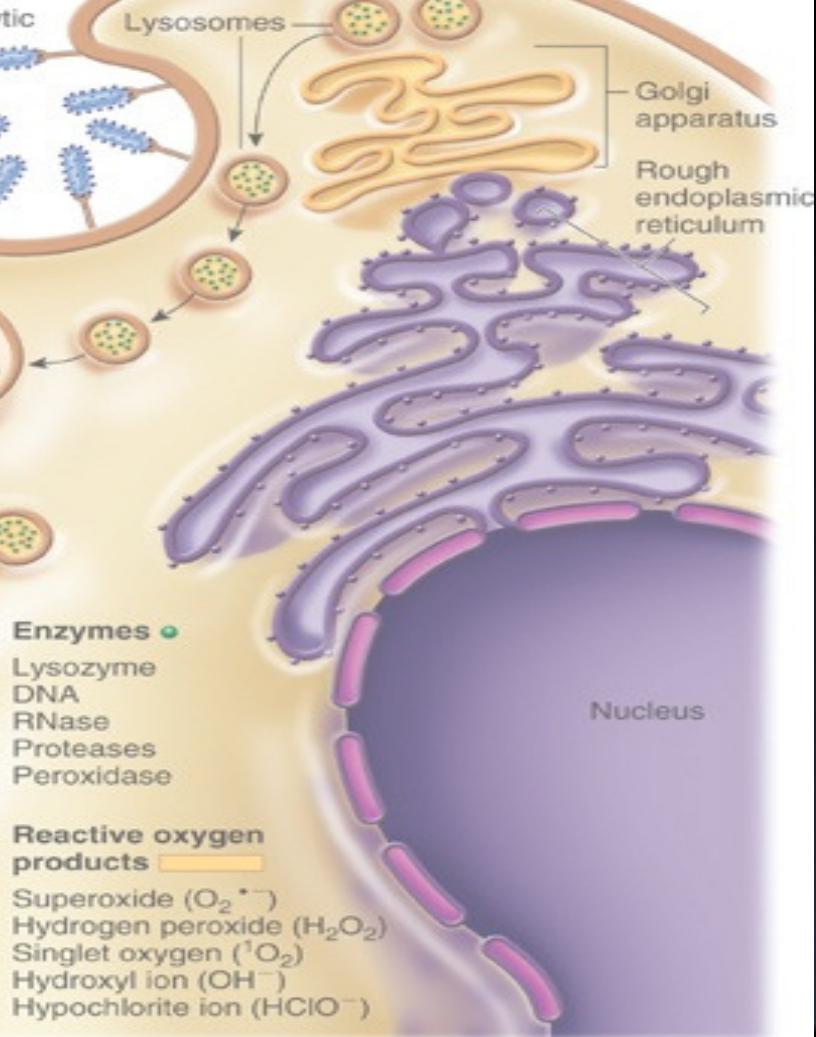


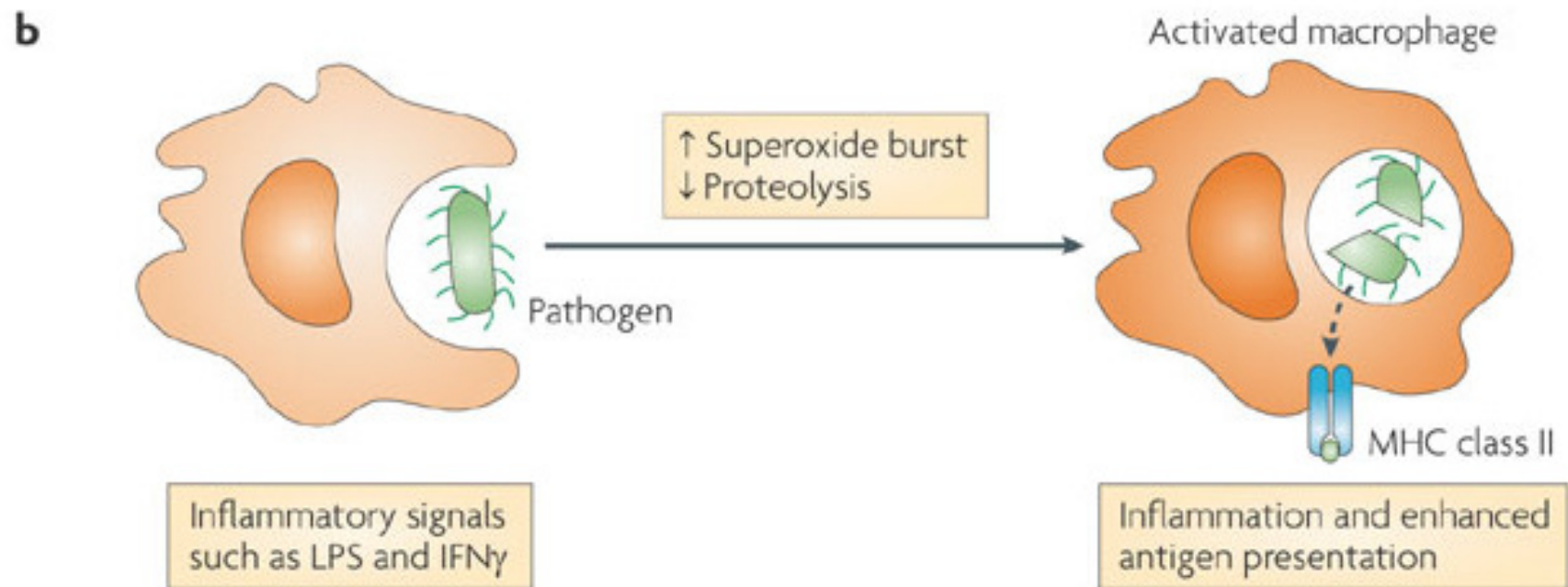
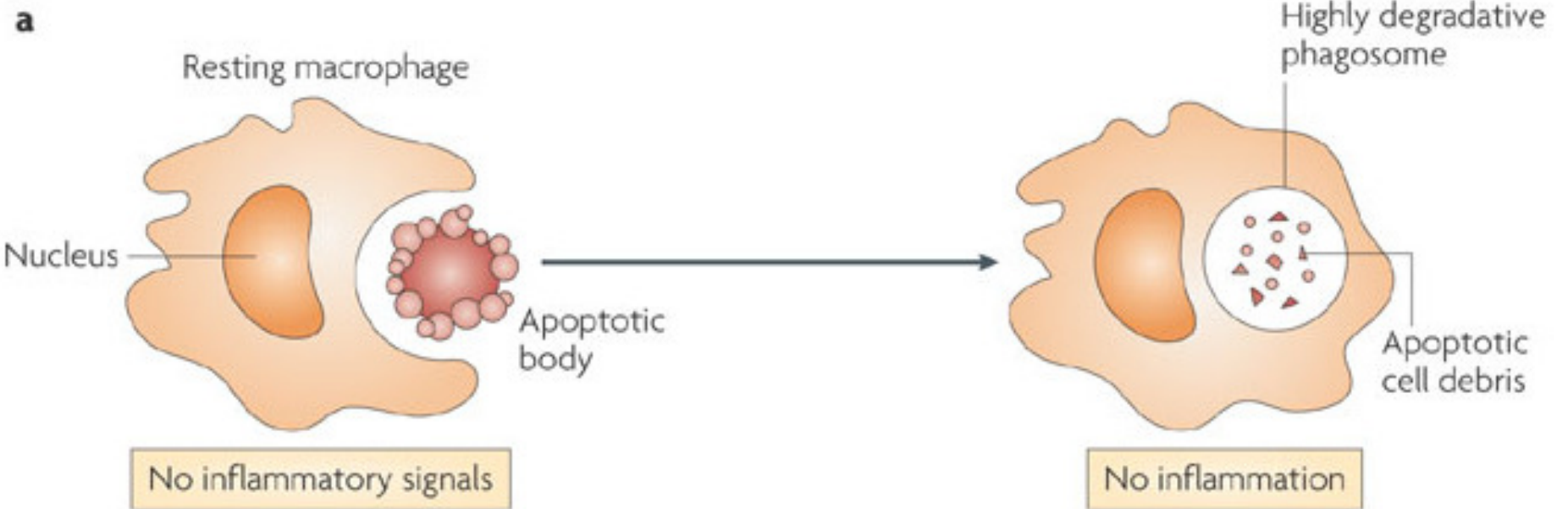
Enzymes ●

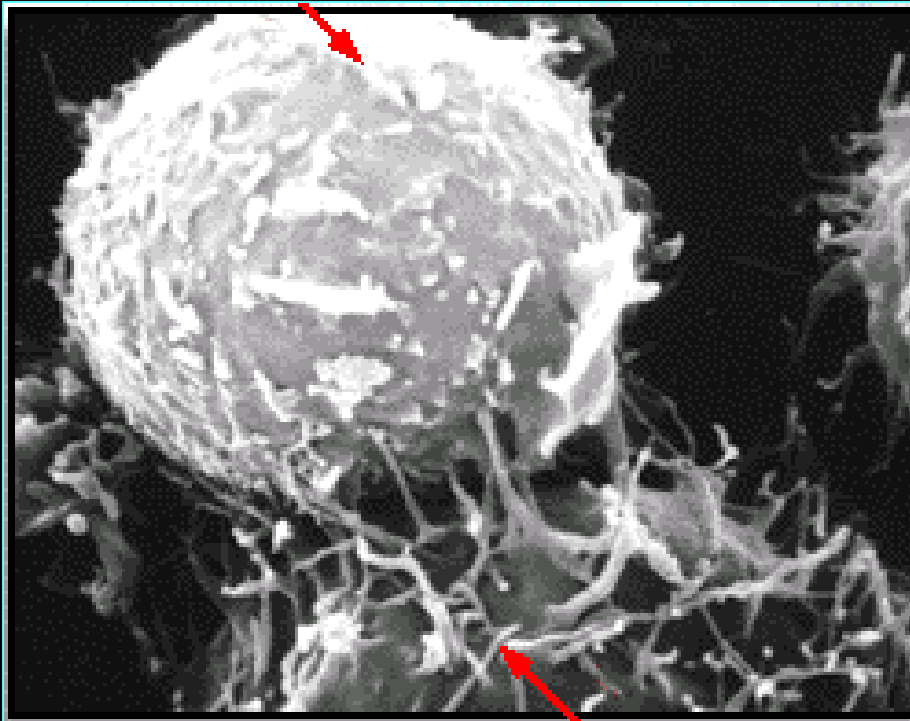
- Lysozyme
- DNAse
- RNase
- Proteases
- Peroxidase

Reactive oxygen products ■

- Superoxide ($O_2^{\bullet -}$)
- Hydrogen peroxide (H_2O_2)
- Singlet oxygen (1O_2)
- Hydroxyl ion (OH^-)
- Hypochlorite ion ($HClO^-$)

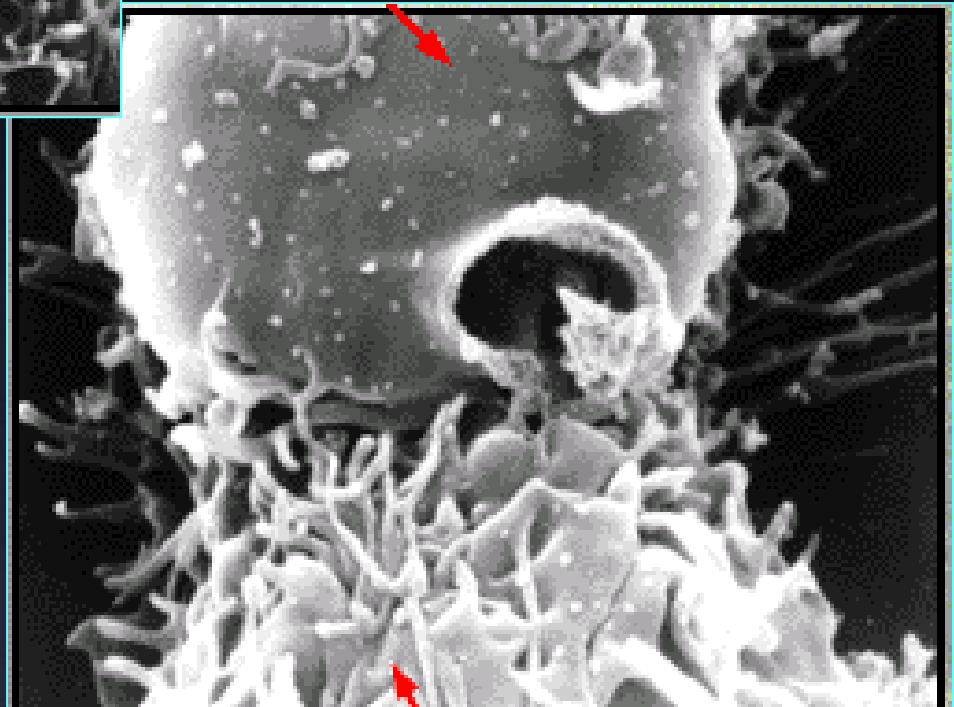






**RESTING
MACROPHAGE**

**ACTIVATED
MACROPHAGE**



A scanning electron micrograph (SEM) of an activated macrophage. The cell is shown in a highly spread, flattened state on a dark surface. It has a long, thin, and irregularly shaped protrusion extending from its main body. The surface of the cell is covered in a complex network of fine, interconnected filaments, giving it a textured, almost crystalline appearance. In the lower right corner, there is a small, bright, elongated object, possibly a bacterium or a piece of debris, which the macrophage appears to be interacting with. The background is a dark, uniform color, likely the substrate the cell is on.

macrophage = *big eater*

**ACTIVATED
MACROPHAGE**

Reticuloendothelial System

Monocytes/Macrophage System

▪ Monocytes when enter the tissues they transform themselves into macrophages this system of phagocytes is called as **Monocyte-Macrophage Cell System**

Examples are: -

1. Skin, mucosa and Subc tissues (Langerhans cell)

2. Lymph Nodes (Sinus histiocytes)

3. Alveolar macrophages

4. Liver sinuses (Kupffer Cells)

5. Spleen & Bone marrow

6. Microglia in Brain

7. Kidneys (Mesangial Cells)

8. Bone (Osteoclasts)

Hofbauer cells in Placenta

Epithelioid cells in Granulomas

Tissue macrophages

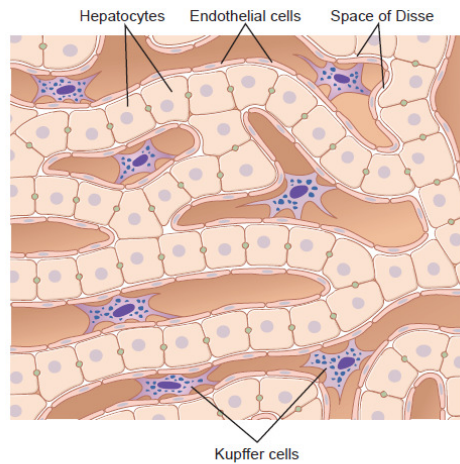


Figure 34-4. Kupfer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupfer cells.

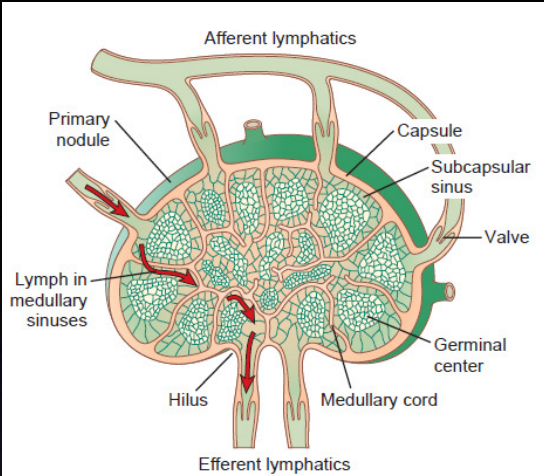
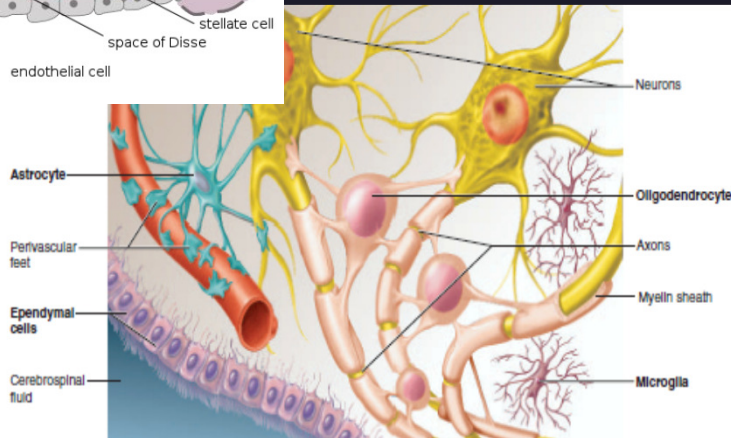
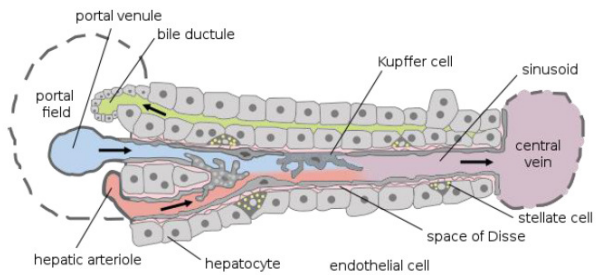
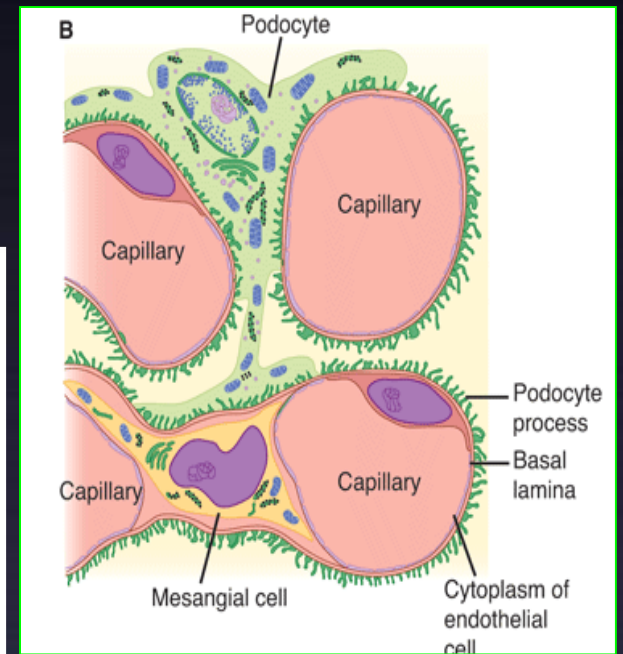
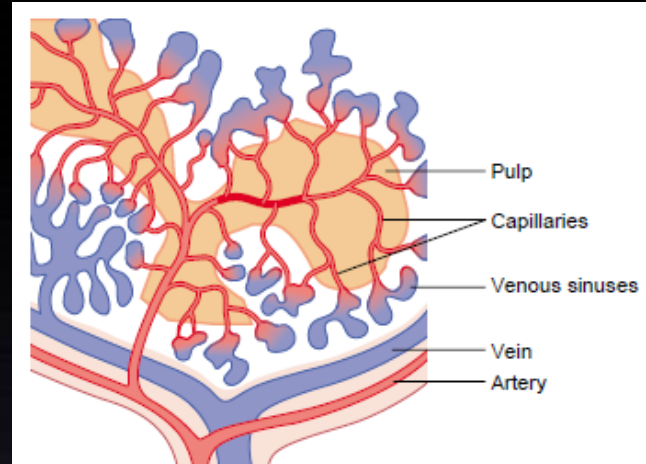
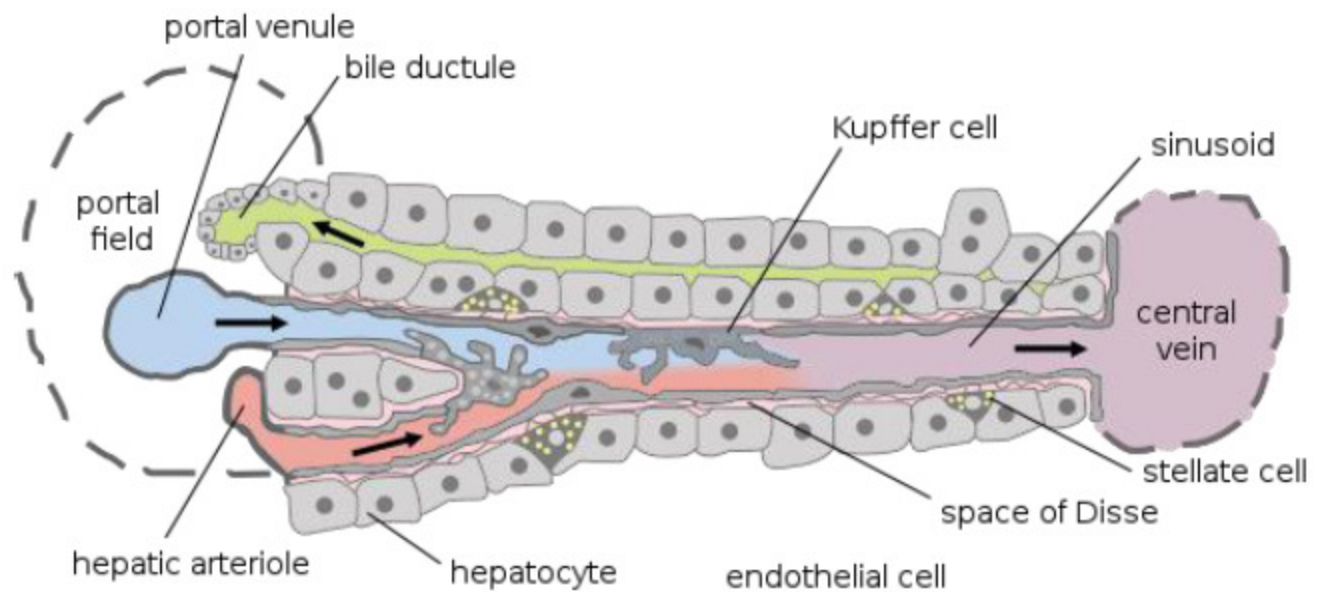
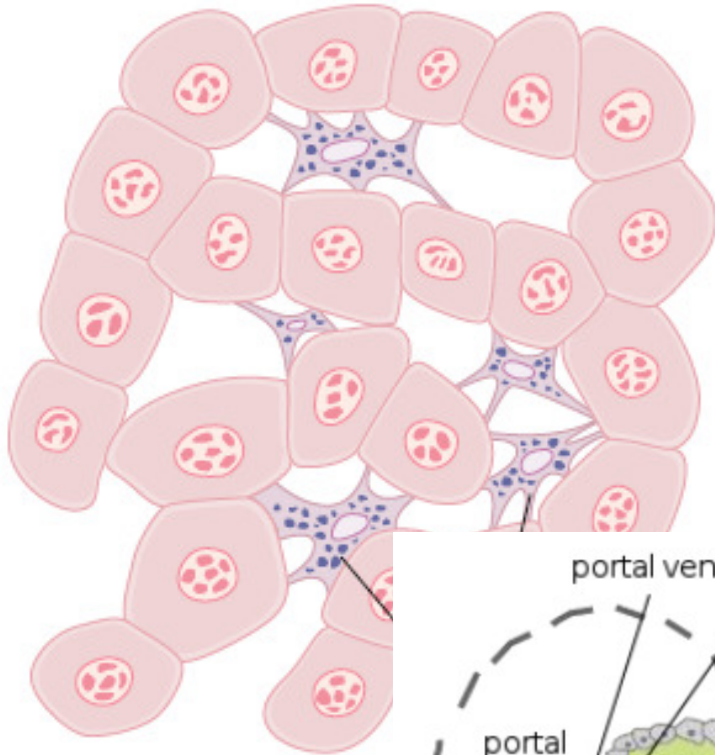


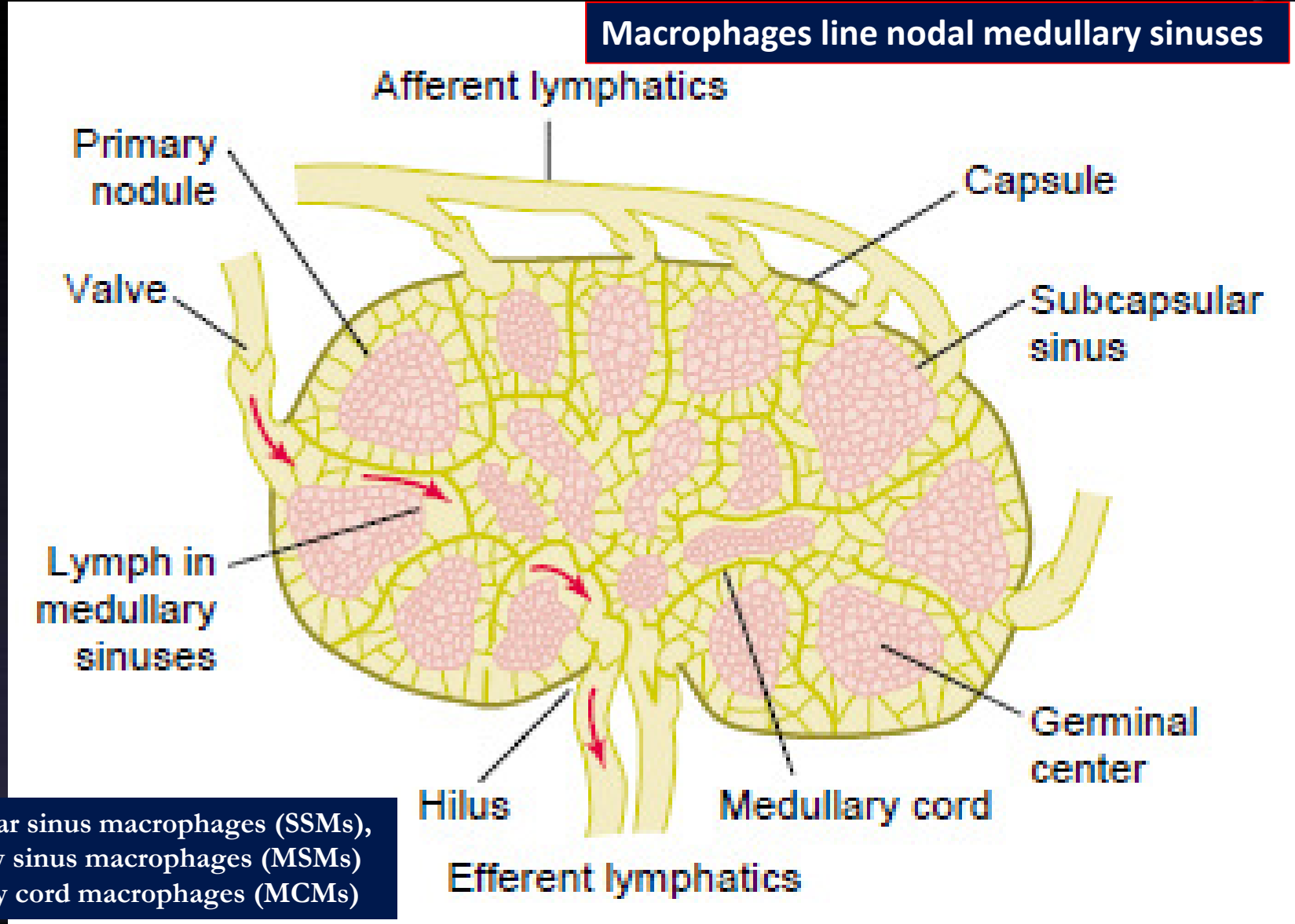
Figure 34-3. Functional diagram of a lymph node.



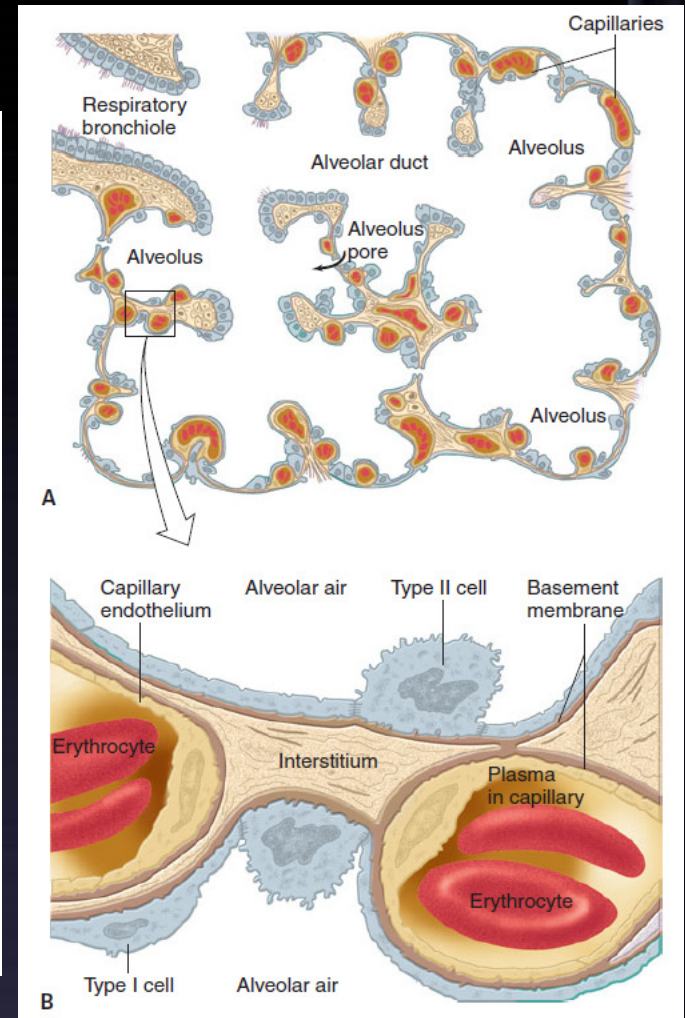
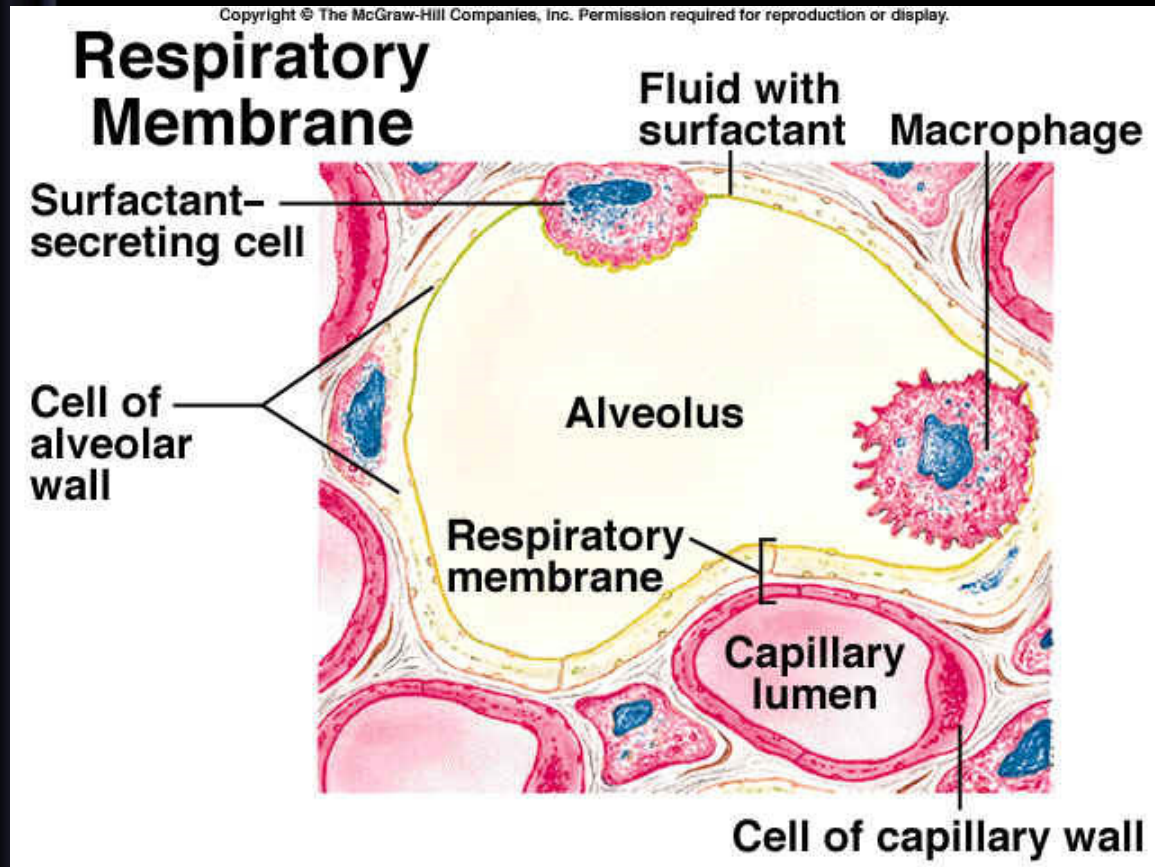
Tissue macrophages in Liver sinuses



Tissue macrophages in Lymph Nodes



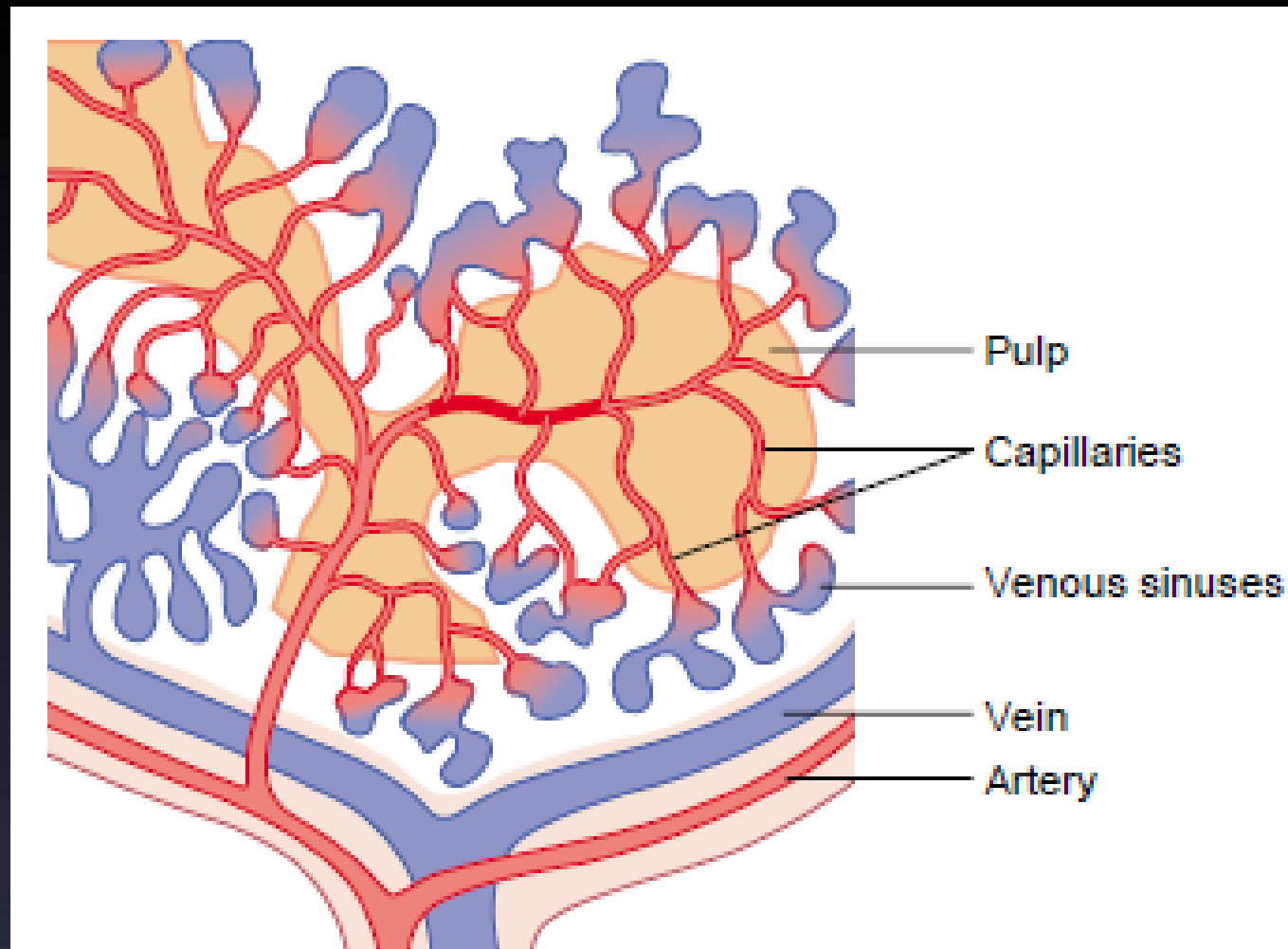
Tissue macrophages in Lungs



“dust cells” because of their content of intracellular carbon particles

Tissue macrophages in Spleen

The blood squeezes through the trabecular cords meshwork of red pulp.

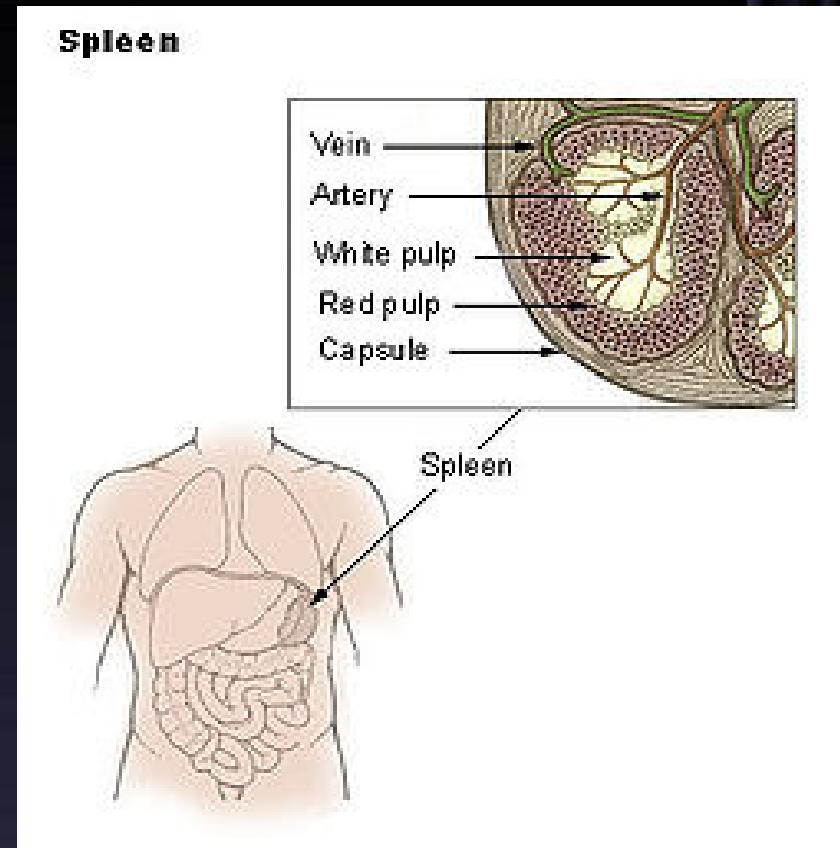


SPLEEN

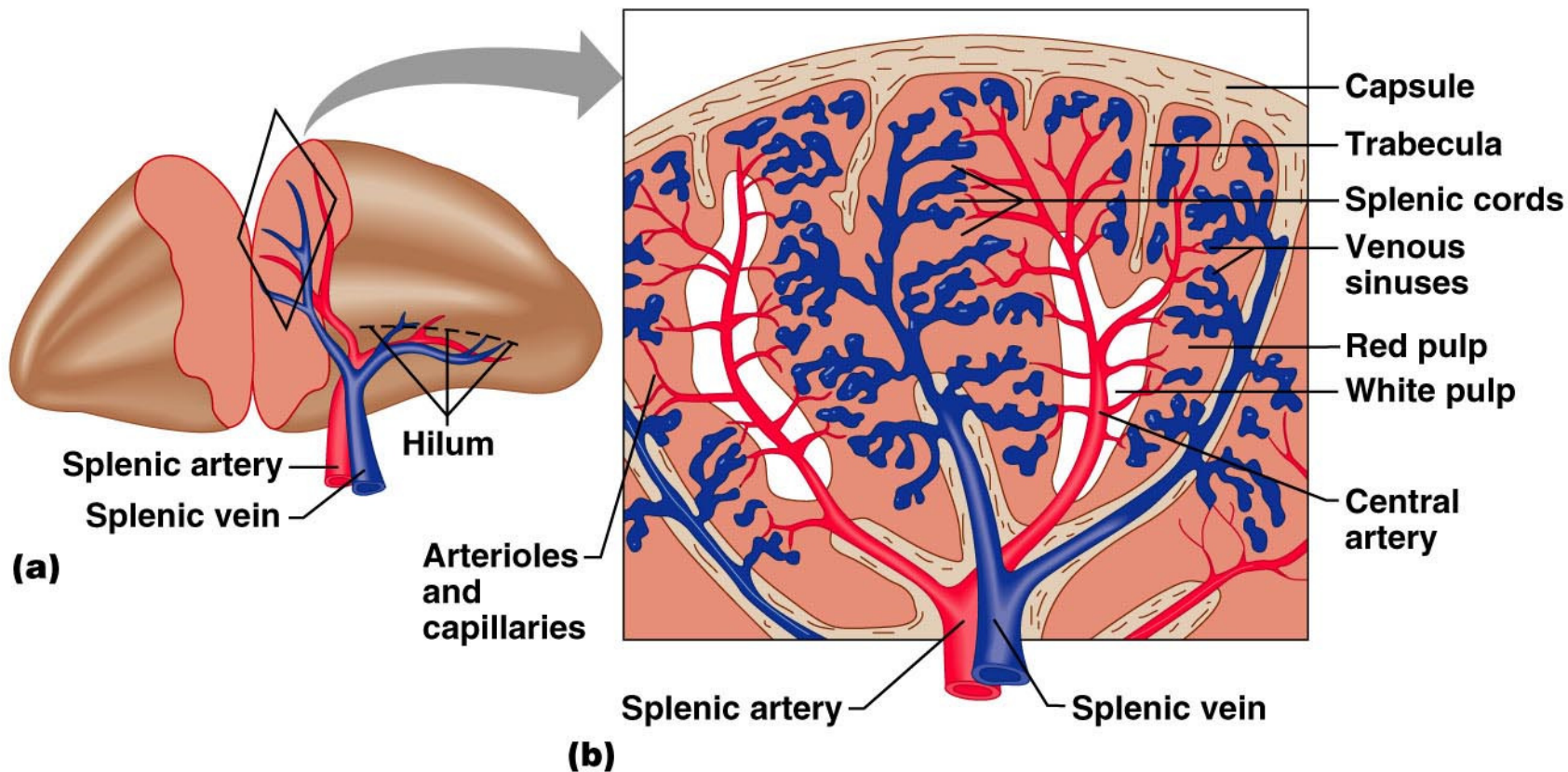
- Is soft **purple gray** in color located in the **left upper quadrant** of the **abdomen**.
- It is a **highly vascular** lymphoid organ.
- It plays an important roles in: **red blood cells** integrity and has **immune function**.
- It holds a **reserve** of blood in case of **hemorrhagic shock**.
- It is one of the centers of activity of the **RES** and its **absence** leads to a **predisposition** toward certain **infections**.
- Despite its importance, there are **no tests** specific to splenic function.

STRUCTURE OF SPLEEN

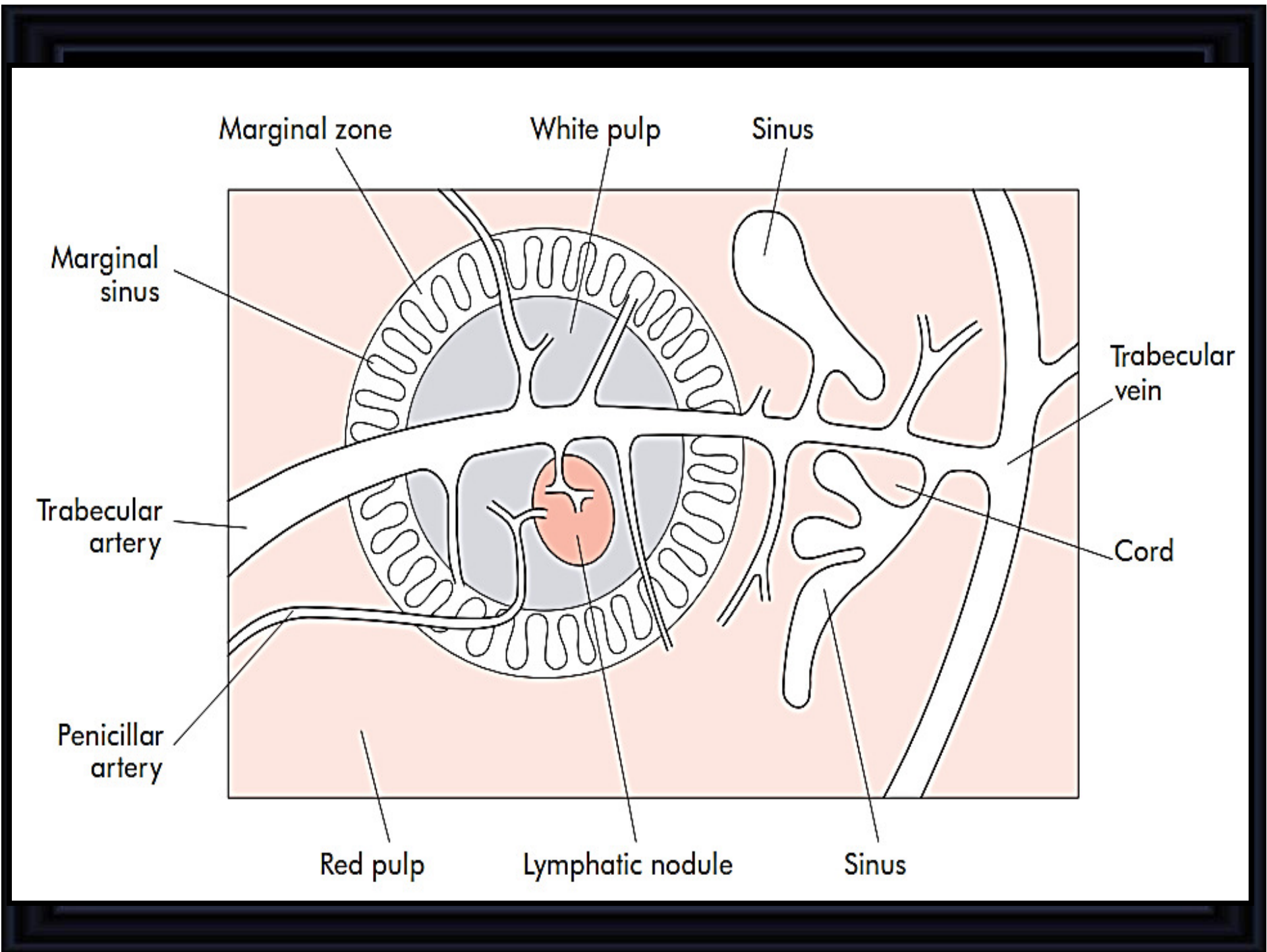
- **White pulp**: Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.
- **Red pulp**: surrounds white pulp, composed of Venous sinuses filled with whole blood and Splenic cords of reticular connective tissue rich in macrophages.

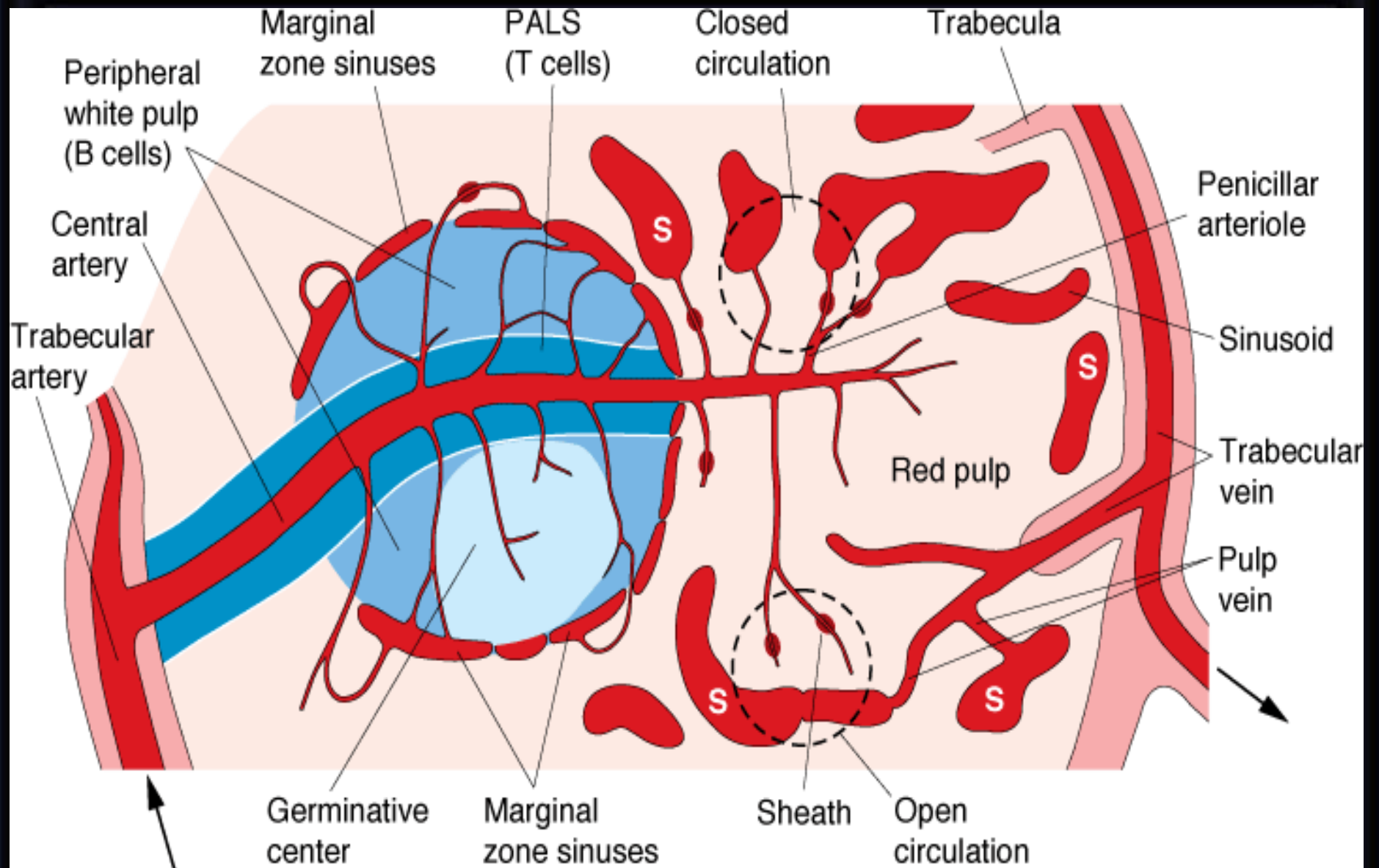


Spleen



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Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition*: <http://www.accessmedicine.com>

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FUNCTIONS OF SPLEEN

Red Pulp- Red Pulp- filtering function

- RBC's able to deform through sinusoidal wall and endothelium
Culling
- Macrophage activation - macrophages filter and destroy foreign material in blood
Macrophage activation

White pulp - immunologic functions

- trapping and processing of antigens
- the major site of antibody synthesis
- key role in removal of encapsulated bacteria (Strep pneumo)

Cytopoiesis:

- From the fourth month of intrauterine life, some degree of hemopoiesis occurs in the fetal spleen.
- Stimulation of the white pulp may occur following antigenic challenge, resulting in the proliferation of T and B cells and macrophages.
- This may also occur in myeloproliferative disorders, thalassaemias and chronic haemolytic anaemias.

FUNCTIONS OF SPLEEN

•Formation of blood cells

- play in important role in the hemopoietic function in embryo
- during the hepatic stage, spleen produces the blood cells along with liver

•Destruction of blood cells

- the older RBCs, lymphocytes & thrombocytes are destroyed in spleen and recycles iron. Increased in hereditary spherocytosis

•Reservoir function

- A large number of RBCs and platelets are stored in spleen and recycles iron
- RBCs are released from spleen into circulation during the emergency conditions like hypoxia & hemorrhage

•Role in defense of body

- spleen filters the blood by removing the microorganism
- macrophages in splenic pulp phagocytose microorganisms & foreign bodies
- spleen contains about 25% of T lymphocytes & 15% of B lymphocytes & form the site of antibody production mainly IgM

FUNCTIONS OF SPLEEN

•Role in defense of body

—**Immune function:**spleen filters the blood by removing the microorganism. Macrophages in splenic pulp phagocytose microorganisms & foreign bodies

- spleen contains about 25% of T lymphocytes & 15% of B lymphocytes
- The spleen processes foreign antigens and is the major site of specific immunoglobulin M (IgM) production.
- The non-specific opsonins, properdin and tuftsin, are synthesized.
- These antibodies are of B- and T-cell origin and bind to the specific receptors on the surface of macrophages and leukocytes, stimulating their phagocytic, bactericidal and tumoricidal activity.

Immune Functions of Spleen

1. Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to **blood-borne antigens**.
2. **Destruction and processing** of antigens.
3. **Reservoir of lymphocytes** in white pulp.
4. Site for **Phagocytosis** of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)

Immune Functions of Spleen cont.

5. Site of **B cell maturation** into plasma cells, which synthesize antibodies in its white pulp and initiates **humoral response**.
6. Removes antibody-coated bacteria along with **antibody-coated blood cells**.
7. It contains (in its blood reserve) half of the body **monocytes** within the red pulp, upon moving to injured tissue (such as the heart), turn into **dendritic cells** and **macrophages** that promoting **tissue healing**.

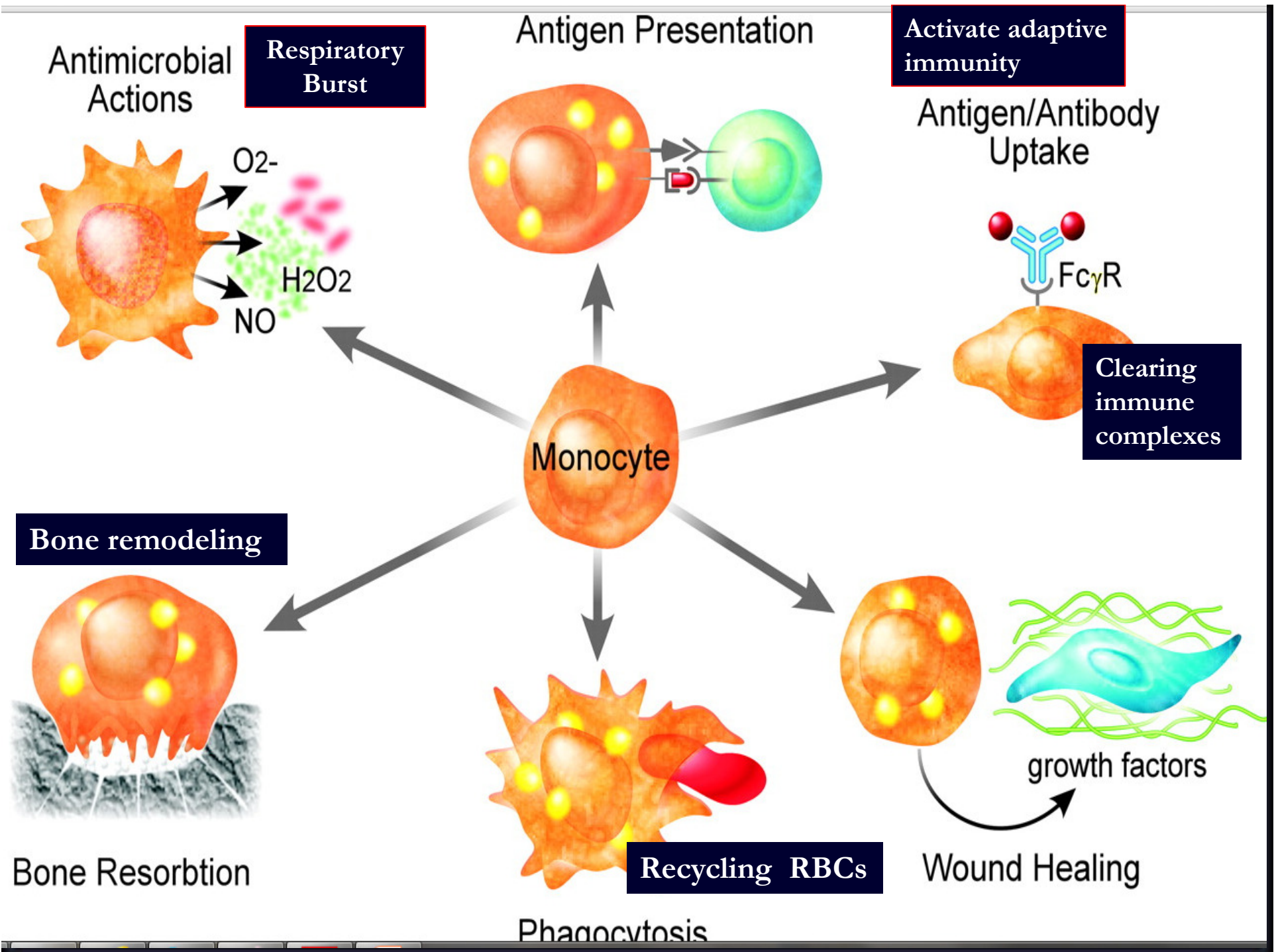
Splenectomy

Indications:

1. **Hypersplenism:** enlargement of the spleen (splenomegaly) with defects in the blood cells count.
2. Primary spleen **cancers**.
3. **Haemolytic anaemias:** Sickle cell anaemia, Thalassaemia, hereditary spherocytosis (HS) and elliptocytosis
4. Idiopathic thrombocytopenic purpura (**ITP**).
5. Trauma.
6. Hodgkin's disease.
7. Autoimmune hemolytic disorders.

Risks & complications of Splenectomy

- ❖ Overwhelming **bacterial infection** or post splenectomy **sepsis**.
- ❖ Patient is prone to **malaria**.
- ❖ Inflammation of the **pancreas** and collapse of the **lungs**.
- ❖ Excessive **post-operative bleeding** (surgical).
- ❖ Post-operative **thrombocytosis** and **thrombosis**.



	Macrophage/Monocyte	Neutrophil
Morphology	Large mononuclear cells with granular cytoplasm	Smaller cells with multi-lobed nucleus and neutral cytoplasmic granules
Location	Often resident in tissues (remove routine cell debris)	Blood – requires recruitment to site of infection
Killing ability	Require activation by bacterial molecules \pm IFN γ	Activated during recruitment, then able to kill internalised bacteria automatically
After killing	Migrate to local lymph nodes	Die at site by apoptosis (then taken up by macrophages)
Antigen presentation	Can present antigen (Class II up-regulated by IFN γ)	Cannot present antigen (don't normally express Class II)